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The Cardiovascular Manifestations of Leptospirosis

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LEPTOSPIROSIS is an uncommon zoonosis caused by any of the almost 170 serotypes of the spirochete *Leptospira interrogans*. Most commonly associated with tropical climates, this disease has been reported from all regions of the United States and most of the world. Most persons infected with this organism have either subclinical disease or a mild anicteric febrile illness, but 5% to 10% of patients will have severe leptospirosis, characterized by jaundice and azotemia. This subset of severely ill patients has what has been called Weil's disease after the physician who first described this illness in 1886.

Previous studies of patients with severe leptospirosis have usually focused on the hepatic and renal manifestations of this illness. Despite the fact that as many as 10% of patients may have associated cardiac involvement,[1,2] these manifestations are seldom discussed in reviews on the clinical aspects of this disease. I describe the case of a patient in whom severe leptospirosis developed with several cardiac changes. A review of both the clinical and pathologic literature that has addressed the many cardiac manifestations of this uncommon disease is also presented.

Report of a Case

The patient, a 42-year-old man, was transferred to a Honolulu, Hawaii, hospital from a rural hospital on a neighboring Hawaiian island where he had been admitted for the treatment of a febrile illness characterized by spiking fevers to 40°C (104°F), severe myalgias, and some mild hallucinations. At that hospital he had been noted to have fever, jaundice, mild hypotension, and thrombocytopenia and had been treated with intravenous penicillin and oral tetracycline therapy for presumed leptospirosis. He was transferred when no improvement was noted by the second hospital day.

The patient said he had no significant travel history or unusual exposures. He had been in good health and was employed as a police officer and part-time construction worker. On physical examination the patient appeared flushed and jaundiced. The temperature was 39.9°C, the pulse rate 140 beats per minute, and the respiratory rate 36 per minute. An initial systolic blood pressure of 80 mm of mercury rose after a fluid bolus. There was a varicelliform rash over the face and neck, and right axillary adenopathy was noted. Bilateral conjunctival suffusion was present. There was no jugular venous distention, and the lungs were clear. Examination of the heart disclosed a tachycardic rhythm and the presence of a third heart sound. The abdomen was normal with no hepatosplenomegaly. Other than severe proximal muscle tenderness, the rest of the examination elicited no abnormalities.

ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
ECG = electrocardiogram

The hematocrit was 0.28, the platelet count was 66×10^9 per liter, and the leukocyte count was 13.5×10^9 per liter with 0.61 neutrophils, 0.34 band forms, 0.04 lymphocytes, and 0.01 mononuclear cells.* Prothrombin and partial thromboplastin times were normal. The blood urea nitrogen level was 8.9 mmol per liter (25 mg per dl; normal, 3.0 to 6.5 mmol per liter); serum creatinine, 195 μmol per liter (2.2 mg per dl; normal, 50 to 100 μmol per liter); total bilirubin, 202 μmol per liter (11.8 mg per dl; normal, 2 to 18 μmol per liter); lactate dehydrogenase, 265 units per liter (normal, 50 to 150); and creatine kinase, 5,914 units per liter (normal, <130). Arterial blood gas measurements with the patient receiving supplemental oxygen showed a pH of 7.47, a P_{CO_2} of 31 mm of mercury, and a P_{O_2} of 119 mm of mercury. An electrocardiogram showed sinus tachycardia with an intraventricular conduction delay and diffuse, nonspecific T-wave changes (Figure 1). A chest roentgenogram showed mild cardiomegaly and diffuse bilateral interstitial infiltrates (Figure 2). Catheterization of the right side of the heart revealed a pulmonary capillary wedge pressure of 13 cm of water, a cardiac output of 7.09 liters per minute, and a calculated systemic vascular resistance of 699 dynes·sec·cm^2. A Gram's stain of the cerebrospinal fluid was negative for organisms.

Serum and urine specimens were obtained for bacterial, viral, and leptospiral cultures and serologic tests, and the patient was treated with intravenous penicillin, doxycycline, and an ampicillin-sulbactam sodium combination. On the second day of admission a bedside echocardiogram showed a mildly dilated left ventricle with an end-diastolic diameter of 5.8 cm. The overall systolic function was mildly depressed with no segmental wall motion abnormalities detected. The shortening fraction was 25%, and a small posterior pericardial effusion was seen.

By the third hospital day the patient noted diminished myalgias and improved strength; at this time the total bilirubin concentration had risen to 279 μmol per liter, but the creatine kinase level had begun to fall. Over the next week the hyperbilirubinemia and elevated creatinine levels returned to normal, the pulmonary infiltrates resolved, and the third heart sound disappeared. The patient was discharged on his ninth hospital day. At the time of discharge all cultures, including both blood and urine for leptospirosis, remained neg-

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*For hematocrit and differential cell count, the values are expressed as a fraction of 1.

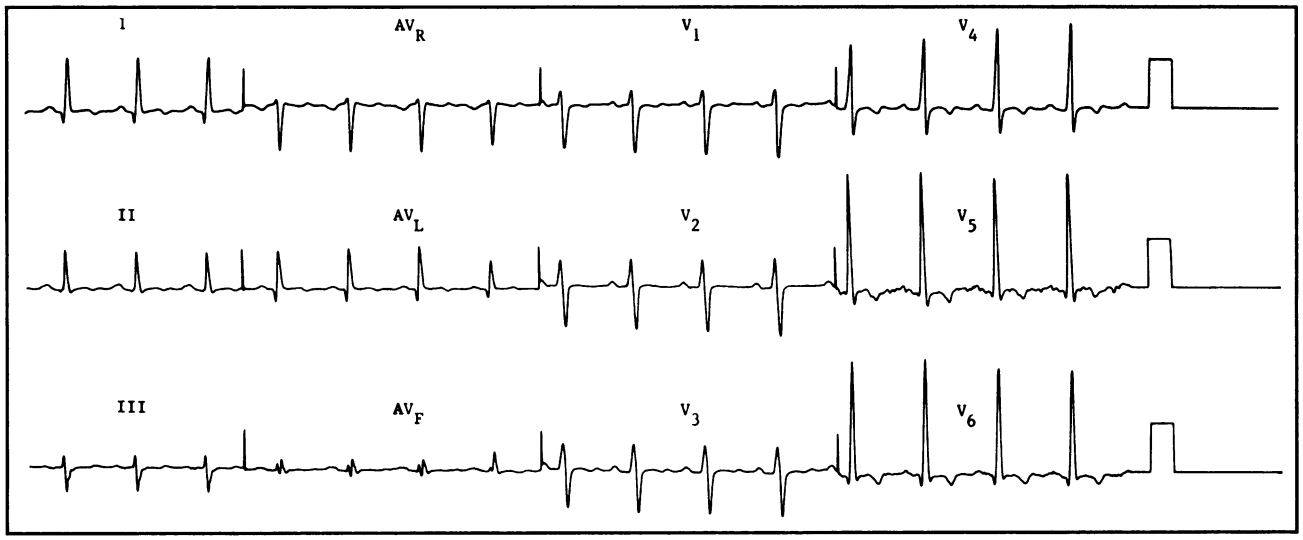

Figure 1.—The electrocardiogram of a patient with leptospirosis shows an intraventricular conduction delay and nonspecific ST-T wave changes.

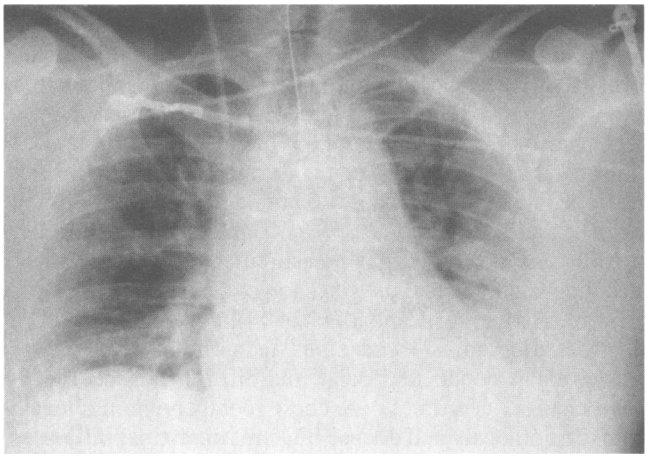

Figure 2.—A chest roentgenogram of a patient with leptospirosis shows cardiomegaly and diffuse bilateral infiltrates.

ative. A microscopic agglutination test for *Leptospira* antibodies was positive at a 1:800 dilution; over 1:100 is consistent with an acute infection. Titers for Rocky Mountain spotted fever, toxoplasmosis, adenovirus, coxsackievirus groups A and B, echovirus, and influenza virus groups A and B were negative for acute infection. Two days after discharge a follow-up echocardiogram showed resolution of the previous left ventricular dilatation and return of the systolic function to normal. The patient has since remained in good health.

Discussion

Leptospirosis, while uncommon, affects people of all age groups from all areas of the world. It is usually acquired through contact with either domestic or wild animals. Frequently exposure occurs from swimming or partial immersion in contaminated water sources. In Hawaii, leptospirosis is more common, and the most important vectors are thought to be rats, mice, and mongooses. Symptoms usually begin several days to several weeks after exposure and range from a mild febrile illness to overt Weil's syndrome with azotemia, jaundice, confusion, anemia, thrombocytopenia, and high temperatures. An aseptic meningitis may also result from infection with this organism.

The incidence of cardiovascular manifestations in patients with leptospirosis remains unknown. In 1951 Sodeman and Killough reported data from 80 patients with leptospirosis, of whom 8 (10%) had definite evidence of cardiac involvement.[1] Hospital-based studies have found even higher rates,[3,4] and postmortem studies have elicited histologic evidence of cardiac involvement in as many as 70% of patients dying of leptospirosis.[5,6] Common to all these studies is the presence of severe systemic disease, often with both renal and hepatic involvement (Weil's syndrome).

In outpatients with leptospirosis, cardiovascular manifestations are seldom observed.[7-9] These patients are usually anicteric and have a low prevalence of renal disease. The reasons why some patients have multiple systemic manifestations of leptospirosis while others remain asymptomatic are unknown.

The case of presumptive leptospirosis described herein illustrates several of the cardiac manifestations that have been associated with leptospirosis, including nonspecific electrocardiographic changes, both clinical and echocardiographic evidence of left ventricular dysfunction, and the development of a pericardial effusion.

Electrocardiographic Abnormalities

Numerous electrocardiographic (ECG) abnormalities have been found in patients with leptospirosis. In the case described, these represented delayed intraventricular conduction and diffusely inverted or flattened T waves (Figure 1). Both intraventricular conduction delay and nonspecific T-wave changes were reported in the study by Sodeman and Killough of 80 cases of Weil's disease.[1] Of their eight patients who had clinical evidence of myocardial involvement, seven had either flattened or inverted T waves on an ECG, most commonly in the anterior or lateral leads.[1] Another study of the ECG abnormalities of leptospirosis noted pronounced anterior ST-segment elevation in four patients.[10] In none of the patients in either study did clinical or laboratory evidence of myocardial infarction develop, and in cases where follow-up information was available, the ECG returned to normal after proper antibiotic therapy. In the latter series the authors postulated a localized myocarditis or pericarditis to explain these ECG findings.[10]

Other ECG changes have also been described. ST-T wave changes characteristic of pericarditis have been found in at least one patient with a leptospirosis-induced pericardial friction rub.[11] Delayed intraventricular conduction or bundle branch blocks have been reported in at least one review[1] but appear to be an infrequent finding. Even children have been found to have nonspecific ECG abnormalities in association with leptospirosis.[3]

Despite these sometimes dramatic changes, the sensitivity of an ECG for identifying myocardial involvement is not high. Of note, several patients with overt pulmonary edema and atrial arrhythmias have been reported to have otherwise normal ECGs.[4]

Arrhythmias

Rhythm disturbances also appear commonly in patients with leptospirosis. A relative bradycardia may be found in many of these patients.[12] The mechanism of this pulse-temperature discrepancy is unclear but has also been reported in association with other infectious diseases. Atrial arrhythmias, including both atrial fibrillation and atrial flutter, are frequently encountered.[3,4,12] Premature ventricular contractions are common, and one case of ventricular tachycardia has been reported.[13] A study of nine children with leptospirosis reported three to have suffered at least one cardiopulmonary arrest during their hospital stay.[3] The antecedent rhythms, clinical findings, and outcome of those three patients were not reported. In addition, both first- and second-degree heart block[14] and junctional rhythms[10] have been described in patients with leptospirosis.

As with the ECG abnormalities, rhythm disturbances associated with leptospirosis usually resolve early in the course of the illness.

Pericarditis

Although leptospirosis-induced pericarditis has been reported in several studies,[11,15-17] the etiology and prevalence remain unclear. The diagnosis has usually been established by the presence of a pericardial friction rub or ECG findings, or both, characteristic of pericarditis. Because of the high incidence of severe renal disease in these patients, the distinction between uremic pericarditis and that which is the direct result of leptospirosis may at times be difficult.[12] Studies correlating the clinical and pathologic findings in these patients have not yet been done.

Congestive Heart Failure

Several authors have described clinical evidence of congestive heart failure in patients with leptospirosis, but this also appears to be an infrequent complication.[1,3,10,13] Studies as early as 1917 have noted transient cardiac dilatation in some patients with this infection.[18] In a review of chest radiography in Jamaican patients with leptospirosis, Lee and coworkers found that 4 of 44 patients (9%) had cardiomegaly.[19] Two of these four patients were thought to have had biventricular enlargement, while the other two had left ventricular enlargement only. On follow-up examination, three of the four patients had their hearts return to normal size, but the fourth had a persistently enlarged heart. In a similar study of 80 patients with Weil's disease in which 8 had clinical evidence of cardiac involvement, 2 had both radiographic cardiomegaly and signs and symptoms of congestive heart failure.[1]

Radiographic evidence of cardiac enlargement can be misleading. Although not yet reported, leptospirosis-induced pericarditis with an associated effusion might also present as cardiomegaly. The case reported here is the first in which there was echocardiographic evidence of left ventricular dilatation with reduced systolic function and a pericardial effusion. This is the modality of choice in determining the cause of cardiomegaly associated with leptospirosis.

Another finding that has been reported is both the radiographic and clinical evidence of pulmonary edema. Both cardiogenic and noncardiogenic pulmonary edema have been described. Several studies with adequate supporting hemodynamic data have shown that the adult respiratory distress syndrome (ARDS) can occur in association with leptospirosis.[20-22] It is likely that increased vascular permeability with a leakage of protein and fluid out of the intravascular compartment is responsible for the ARDS seen in these patients, but neither a specific circulating toxin nor intrapulmonic spirochetes have yet been isolated from patients with leptospirosis.[23,24]

Cardiogenic pulmonary edema occurs more frequently than does ARDS in patients with leptospirosis. The severity of this may range from an asymptomatic radiographic finding to overt cardiogenic shock with acute pulmonary edema.[10,13] Several studies report radiographic evidence of cardiogenic pulmonary edema,[4,13,25] but it must be remembered that this is difficult to distinguish from ARDS or hemorrhagic pneumonitis by chest radiography alone. Hemodynamic data or echocardiographic evidence of left ventricular dysfunction is required to adequately distinguish between these disorders.

Pulmonary edema appears to be a more common finding in patients with oliguric renal failure.[4,25] Whether this reflects a cardiogenic cause or volume overload has not been identified. In this population, invasive hemodynamic monitoring with a pulmonary artery catheter may also be useful in distinguishing between these various pathophysiologic processes.

Pathologic Findings

Involvement of the heart is a common postmortem finding in those patients who die of leptospirosis. Autopsy studies have reported histologic evidence of myocarditis in 50% to 100% of those hearts studied following death from this infection.[5,6,26] Involvement may range from small areas of focal inflammation to diffuse inflammation with interstitial edema. The inflammatory component consists primarily of lymphocytes and plasma cells; leukocytes are usually seen only in small numbers.[6] These inflammatory infiltrates are most commonly detected in the atria, atrioventricular region, and the interventricular septum.[5] In addition, petechiae or larger areas of hemorrhage may be found in as many as 80% of patients, most conspicuously in the epicardium but also occasionally in the endocardium or myocardium.[6] In one study of 33 postmortem examinations, 8 hearts were involved to the extent that cardiac failure was thought to have contributed to the patients' demise.[26]

When myocarditis is present, inflammation of the conduction system almost always exists.[5,6] To date, no correlation between postmortem findings and antemortem rhythm disturbances has been attempted.

Aortitis, with marked infiltration of lymphocytes and plasma cells into the aortic adventitia, has been found in 58% of the autopsies in one study.[5] This inflammation occurs

chiefly about the vasa vasorum of the aortic adventitia, with extension into the outer media.[5,26] Acute coronary arteritis, affecting the main branches of the coronary arteries, is even more common. DeBrito and colleagues found this in 14 of the 20 autopsies (70%) they performed for fatal leptospirosis.[5] Despite substantial inflammation, actual thrombosis of the coronary arteries was rare.[5] They also found that the presence of coronary arteritis closely correlated with histologic evidence of interstitial myocarditis.[5]

Valvular involvement may also occur in leptospirosis.[5] Two cases of vegetative endocarditis due to *Leptospira icterohaemorrhagiae* have been found at autopsy, but this is clearly an exceedingly rare phenomenon.[27]

Despite the clinical diagnosis of pericarditis in numerous patients with leptospirosis, autopsies usually fail to find significant pericardial inflammation. Whether an underlying epicarditis has been responsible for the pericardial friction rubs heard in these patients remains unknown.

Conclusion

A wide variety of cardiac manifestations may be seen in patients with severe leptospirosis. The mortality of these patients, who usually have both jaundice and azotemia, has been reported to range from 15% to 40%.[23,28] Despite myocardial involvement, death is usually the result of either renal or hepatic dysfunction.[28] Regardless of this, patients with severe leptospirosis should be closely observed for the development of cardiac involvement. Echocardiography or invasive hemodynamic monitoring may be useful tools in the management of either cardiomegaly or diffuse pulmonary infiltrates. With the prompt initiation of intravenous penicillin therapy, which is effective even when begun late in the course of the disease, it is hoped that the high mortality seen in these patients can be significantly reduced.[29]

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Adrenal Ganglioneuroma-Pheochromocytoma Secreting Vasoactive Intestinal Polypeptide

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THE RARE SYNDROME of watery diarrhea, hypokalemia, and achlorhydria (WDHA) is presumed to be due to hypersecretion of vasoactive intestinal polypeptide (VIP).[1] In adults, this syndrome is most commonly caused by hyperplasia, adenoma, or carcinoma of the pancreatic islet cells, but it may also occur in patients with bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma, and pheochromocytoma.[2] In contrast, neurogenic tumors such as ganglioneuroma and neuroblastoma are its most common cause in children.[3]

In this report we describe the case of an adult with the WDHA syndrome who in addition had hypercalcemia, hypercalciuria, hypertension, and hyperglycemia. The lesion was located in the right adrenal gland by computed tomographic (CT) scan, and elevated catecholamine secretion was recorded. The cause was an adrenal ganglioneuroma-pheochromocytoma secreting VIP and catecholamines.

Report of a Case

The patient, a 61-year-old man, was referred for evaluation of renal calculi. When seen, however, his major symptoms were chronic watery diarrhea and episodes of flushing.

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